

# XIV.

## National Institute of Environmental Health Sciences

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### INTRODUCTION

The National Institute of Environmental Health Sciences (NIEHS) is located in Research Triangle Park, North Carolina. Since its creation in 1966, the Institute has been the primary source of Federal efforts to study how environmental factors affect human health. Because of the broad scope of the NIEHS mission, its research relies on essentially every discipline in the biological, chemical, and physical sciences.

NIEHS, as part of the National Institutes of Health (NIH), is dedicated to reducing the burden of environmentally associated diseases and dysfunctions. Through a multidisciplinary biomedical research program, disease prevention and intervention efforts, and communication and education programs, the Institute strives to have a significant impact on human health.

Human health and disease result from three interactive elements: environmental factors, genetic susceptibility, and time or age. From conception to death, we are all exposed to a multitude of environmental agents with the potential to disrupt normal physiological function and cause disease. Critical to establishment and maintenance of a healthy human environment is an understanding of the biological basis of these hazards. Without such understanding, we can only guess about which human exposures should be controlled and at what levels.

The opportunity to make a difference in the environmental health sciences has never been greater. A rapid transition in the discipline, coupled with advances in genetic research, has brought scientists near to a breakthrough in the bottleneck of our lack of knowledge about the identity and mechanisms of environmental hazards that contribute to human illness. We are now poised to make enormous progress in prevention, diagnosis, and treatment of diseases associated with environmental factors. The goal is to learn which environmental or genetic

components are the most important contributors to a specific disease and which individuals are most likely to develop that disease.

Environmental health problems are not perceived as local in scope or short term in nature. The most difficult issues stem from a dearth of data and understanding about the health consequences of long-term, low-level exposures to environmental agents. Environmental problems have global effects on human health that may not be easily reversible or amenable to quick technological fixes. Assessing the complex environmental health problems facing today's society requires international cooperation on an unprecedented scale. NIEHS continues to take a leading role in conducting international collaborative research, training, and information exchange in environmental health.

### HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

#### Biological Assay for Estrogenic Activity of Environmental Chemicals

NIEHS intramural scientists participated in worldwide efforts to validate a uterotrophic assay—a biological assay for estrogenic activity of environmental chemicals. Approximately 20 laboratories around the world provided data on the weight of uteruses of rats that received multiple doses of various test substances. Two NIEHS scientists analyzed the data and reported on the following questions:

1. Did each laboratory find uterotrophic effects of the test chemical(s)?
2. Are the laboratory results consistent regarding the magnitude of the effects and the dose levels at which the effects first appeared?
3. Are some of the four protocols more sensitive than others?

4. Did each of the two routes of administration produce consistent results?

Phase I of the study, which evaluated the assay by using a single positive control with known estrogenic activity, was conducted in fiscal year 2000 (FY 00). An independent statistical analysis of uterine response was performed on uterine weights provided by 19 laboratories in 41 experiments carried out as part of the process for validating the assay. The four protocols were as follows:

- Protocol A (16 laboratories)—administration of test chemical to immature rats by oral gavage;
- Protocol B (12 laboratories)—subcutaneous injection of test chemical into immature rats;
- Protocol C (9 laboratories)—subcutaneous injection of test chemical into adult ovariectomized rats for 3 days; and
- Protocol C' (4 laboratories)—subcutaneous injection of test chemical into adult ovariectomized rats for 7 days.

The test chemical was estrogen 17-ethinyl estradiol, and standard doses for each protocol were specified. The protocols also were intended to demonstrate the ability to detect estrogen antagonists by challenging known estrogenic agents.

In phase II, a variety of chemicals having weaker uterotrophic activity were evaluated both in an open dose-response protocol and in a blinded multichemical protocol. The investigators used the same animal models and routes of administration as in phase I. In phase II, two questions were added: (1) Were the results in the blinded protocol consistent with those in the open protocol? (2) Were the results from phases I and II consistent for each laboratory?

### Genetics of Chemically Induced Lymphomas

An intramural researcher has carried out a very productive series of collaborative studies with a laboratory at Linköping University, Sweden. These studies were designed to

define molecular genetic alterations that give rise to chemically induced lymphomas in mice. The researchers have examined lymphomas induced in mice by 1,3-butadiene, because it is a suspected human carcinogen with widespread occupational and environmental exposures. The agent 2',3'-dideoxycytidine was also tested. This compound has been approved for treatment of patients with human immunodeficiency virus (HIV), even though it causes lymphomas in mice.

In the initial study of these mouse lymphomas, the researchers determined allelotypes by using microsatellite markers to map potential tumor-suppressor genes involved in chemically induced lymphomagenesis. This analysis revealed losses of heterozygosity on chromosomes 4 and 11, suggesting inactivation of genes for members of the p16 cyclin-dependent kinase inhibitor family on chromosome 4 and inactivation of the p53 tumor-suppressor gene on chromosome 11. In a subsequent study, the researchers demonstrated a variety of inactivating mutations in the p53 gene of these lymphomas. They also identified a mutation specific to 1,3-butadiene in codon 13 of the *K-ras* oncogene that had been observed in butadiene-induced lung tumors. Next, the researchers examined the p16 gene family and showed that those tumor-suppressor genes can be inactivated by homozygous deletions, as well as hypermethylation of the promoter region. Because the cyclin-dependent kinase inhibitors are a key part of the retinoblastoma pathway, the researchers also examined several additional components of this pathway, including the genes for cyclin D1, cyclin-dependent kinase 4, and retinoblastoma. Surprisingly, no genomic alterations were detected in these genes.

## **SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES**

### **County-to-Country Activities and Bilateral Agreements**

#### **Argentina**

In FY 00, NIEHS collaborated with an investigator from the Institute for Biology and Experimental Medicine, Buenos Aires, in preparations to produce mice with knockout of a gene involved in epididymal maturation that is expressed specifically in the epididymis.

#### **Australia**

A researcher from Australia worked to determine the importance of the CYP2C9 gene in human metabolism of drugs.

#### **Austria**

NIEHS hosted a scientist from the University of Salzburg for 1 month to collaborate on a pilot study of K<sup>+</sup> channel regulation by oxidative stress. This joint research is expected to continue.

#### **Belgium**

In a collaborative study, a scientist at the Faculty of Agronomy, Gembloux, Belgium, investigated interactions among bovine leukemia virus, human T-cell leukemia/lymphoma virus (HTLV), and tristetraroline (TTP) in the pathogenesis of bovine leukemia.

#### **Canada**

Investigators at the University of Western Ontario, London, Ontario, worked jointly with NIEHS to examine the role of DNA methylation in the expression of the BRCA1 gene in breast cancer cells. This project is a long-standing effort, and a report on the study has been submitted for publication in *Oncogene*.

A researcher at McGill University, Montreal, Quebec, is performing studies of the PHAS-I knockout mice developed at NIEHS, to investigate genetic modifiers of insulin action.

A scientist at the University of British Columbia, Vancouver, is collaborating with NIEHS in mapping genes for susceptibility to neural tube defects and modifiers of these genes.

Two NIEHS investigators are using data collected by Health Canada, Ottawa, Ontario, to examine patterns of exposure to organochlorines. The Canadian investigators measured a number of insecticides and congeners of polychlorinated biphenyls (PCBs) in national samples of breast milk. They are now examining the correlation of these chemicals with incidence of disease.

An NIEHS researcher is collaborating with a researcher at the Montreal Neurological Institute to explore the role of intersectin adaptor protein in regulation of signal transduction pathways. Intersectin is composed of modular protein recognition domains, including two Eps15 homology domains at

the N terminus, followed by a coiled-coil domain, and then five Src homology 3 (SH3) domains. Intersectin is able to link mitogenic signaling pathways with the endocytic pathway. Furthermore, the SH3 domains are able to inhibit activation of mitogen-activated protein (MAP) kinase by epidermal growth factor. The researchers demonstrated that intersectin coupled to the *ras* guanine nucleotide exchange factor and that the inhibitory activity of the SH3 domains is due to inhibition of this factor, thereby blocking *ras* activation. These results were published in the *Journal of Biological Chemistry*.

#### **France**

The Acting Chief, Laboratory of Pulmonary Pathobiology, NIEHS, collaborated with the Director of Research at Hôpital Necker-Enfants Malades, Paris, France, to investigate the role of a nuclear hormone receptor, ROR- $\gamma$ , in thymocyte maturation.

#### **Germany**

NIEHS scientists are collaborating with scientists at institutions in Germany on the following research projects:

GSF (Forschungszentrum für Umwelt und Gesundheit) National Research Center for Environment and Health, Neuherberg—examination of the effects of low-dose irradiation in yeast models;

Institute of Clinical Biochemistry and Pathobiochemistry, Medical University Clinic, Würzburg—investigation of p38 kinase-TTP interactions, with use of TTP knockout mice;

University of Berlin—study of *Xenopus/Amphioxus* collections and cross-hybridizations analyzed by expressed sequence tags (EST);

Institute for Pharmaceutical Biotechnology, University of Heidelberg—exploration of the mechanism of xenobiotic transport in brain, focusing on brain capillaries and the choroid plexus;

University of Karlsruhe—investigation of the effects of genistein and daidzein, two phytoestrogens from soy, on the developing reproductive tract; and

University of Göttingen—study of xenobiotic transport and elimination.

#### **Greece**

Investigators at NIEHS and the Institute of Immunology, Biomedical Sciences Research

Center "Alexander Fleming," Vari, worked together on comparisons of the TTP knockout mice developed at NIEHS and the tumor necrosis factor (TNF) and TNF receptor knockout and knock-in mice developed by the Greek investigator.

### **Israel**

Researchers at NIEHS and the Weizmann Institute of Science, Rehovot, investigated the MARCKS and MLP genes in animal models of lissencephaly syndromes.

### **Italy**

A scientist at the University of Rome is collaborating with NIEHS to characterize a mutation in *Drosophila* that causes telomeric repeat arrays to grow to great lengths. All chromosome ends are affected similarly and accumulate both families of telomeric transposons. The genetic factor responsible maps to a single site in the middle of chromosome arm 3R. Another scientist at the University of Rome is exploring the effects of environmental estrogens on development of bone tissue.

### **Japan**

NIEHS investigators are collaborating with investigators at Japanese institutions on the following research projects:

- Tottori University—to determine and study the function of genes for senescence and imprinting;
- University of Kyoto—to identify and characterize novel cytoskeleton proteins important for tumor cell adhesion;
- National Institute of Animal Health, Tsukuba—to identify proteins associated with recombination hot spots and their roles during meiotic recombination in pachytene spermatocytes; and
- Gene Research Center, Okayama University—to elucidate the role of DNA mismatch repair in protecting cells against the mutagenic consequences of base analogue mutagens.

In addition, collaborating researchers at NIEHS and the University School of Medicine, Chiba, determined that at least three mRNA (messenger RNA) splice variants are expressed at specific stages of germ cell development and that these variants are produced by alternative use of three exons and use of unique exon splice sites. This research

began while the Japanese researcher was a Visiting Scientist at NIEHS.

Scientists at the Brain Science Institute, Riken Institute, Saitama, continue to collaborate with NIEHS to uncover the function of bone morphogenetic protein (BMP) signaling for brain function, by inactivating BMP signaling in specific regions of adult mouse brain. The findings from this study may have implications for BMP function during brain development.

An NIEHS investigator collaborated with a Japanese investigator at Kansai University, Moriguchi, to study the role of IP3 receptors in capacitative calcium entry, a mechanism of calcium entry into cells that is linked to phospholipase C activation in a wide variety of cell types. It is not known whether IP3 and the IP3 receptor participate in this pathway. Much of the evidence for their involvement is based on the action of a pharmacological reagent, 2-APB, which is thought to be a specific inhibitor of IP3 receptors. The Japanese investigator produced a DT40 B-cell line with the genes for all three types of IP3 receptors disrupted by targeted homologous recombination. These cells lacked any IP3 binding activity and lost all ability to respond to B-cell receptor activation, a response known to be dependent on IP3 receptors. However, their capacitative calcium entry remained normal. In addition, 2-APB was still able to block the calcium entry, indicating that the mechanism for this function does not involve IP3 receptors. The work has been submitted for publication to the *Journal of Biological Chemistry*.

### **Mexico**

In FY 00, an NIEHS researcher started a joint study with the Chief of the Department of Outdoor Health, University of Mexico City, to identify components of air pollution particulates that cause adverse respiratory effects.

In addition, scientists at NIEHS collaborated with the National Institute of Public Health, Cuernavaca, to investigate the effect of the antiandrogen DDE, a metabolite of dichlorodiphenyltrichloroethane (DDT), on anthropometric measures at birth, and with the National Institute of Public Health and Hospital Infantil Fredrico Gomez, Mexico City, to study early life factors in childhood respiratory illness.

### **The Netherlands**

An NIEHS investigator began a collaborative study with an investigator at the National Institute of Public Health and the Environment, Bilthoven, to examine effects of in utero exposure to hexachlorobenzene in offspring of the Sprague-Dawley rat.

Researchers at the University of Nijmegen are collaborating with NIEHS to study the regulation of xenobiotic excretion in renal proximal tubule by endothelin. This hormone is released by the tubules during injury, and release of endothelin and decreased xenobiotic excretion appear to be early events in the actions of several nephrotoxins.

An NIEHS scientist completed a collaborative project with scientists from the National Institute of Public Health and the Environment, Bilthoven. In this project, entitled Phenolic Phytoprotectants—Role in Preventing Initiation and Progression of Cancer, the scientists used transgenic animal models. Consideration is being given to additional collaborative studies under a European Union Project—The Role of Dietary Phytoestrogens in Prevention of Breast and Prostate Cancer.

### **Norway**

The Chief, Epidemiology Branch, NIEHS, worked with an investigator at Haukeland Hospital, Bergen, and the Norwegian Medical Birth Registry to examine the data on fathers with malformations who have babies with no malformation. The Norwegian Registry is a unique resource that links medical and birth records through personal identifiers.

### **Poland**

An NIEHS researcher collaborated with a researcher at the Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, on a joint project aimed at investigating the fidelity of leading and lagging replication of DNA strands in the bacterium *Escherichia coli*. This work has revealed distinct differences in the fidelity of the two types of replication, presumably related to the different enzymology of the two replication modes. This collaboration has yielded two publications in the *Proceedings of the National Academy of Sciences*.

## Russia

A scientist at NIEHS is collaborating with a scientist at the Russian Academy of Sciences, St. Petersburg, to characterize telomere–telomere interactions in *Drosophila* that have been observed cytologically. They have shown that disruptions of homologous or even nonhomologous telomeres cause derepression of transgenes that were subject to the effects of telomeric position. This finding suggests that telomeric interactions are important for heterochromatin formation around telomeres and possibly for regulation of telomere length.

Investigators at St. Petersburg State University worked with NIEHS in a project supported by a collaborative research grant from the North Atlantic Treaty Organization. The research team investigated the mechanisms underlying the toxic and mutagenic effects of base analogue mutagens and discovered a novel detoxification mechanism for certain base analogues. This mechanism involves newly discovered activities that require the molybdenum cofactor. A report on the work was published in the *Journal of Bacteriology*.

## Spain

An NIEHS researcher works with a researcher at the University of Barcelona (a) to study the expression of the alpha and beta isoforms of the glucocorticoid receptor in a human bronchial epithelial cell line and (b) to explore the regulation of these isoforms by dexamethasone.

The Chief, Laboratory of Molecular Genetics, NIEHS, is collaborating with a scientist at Instituto Nacional de Investigacion y Tecnologia Agraria y Alimentaria, Carretera de La Corua, Madrid, on a study of mutations in RNA viruses. The scientists have developed the first good mutation-reporter system and the best characterization of spontaneous mutation in an RNA virus to date.

## Switzerland

An NIEHS investigator worked with an investigator at the University of Zürich to study the expression of the MARCKS and MLP genes in interstitial cells of normal kidneys and of kidneys with fibroproliferative diseases, in mice.

## Ukraine

Two NIEHS scientists worked with scientists at the Institute of Pediatrics, Obstetrics, and Gynecology, National Medical University, and Kiev Medical Academy of Post-Diploma Education, all in Kiev, on pilot studies to evaluate the feasibility of investigating the relationship of environmental pollutants to reproductive health in Ukraine. They studied reproductive outcomes in a geographic cohort of pregnant women in two urban areas of Ukraine and measured a spectrum of pollutants in biological samples from a subsample of the cohort.

## United Kingdom

Investigators at NIEHS are collaborating with investigators at institutions in the United Kingdom on the following research projects:

- Sanger Centre, Cambridge, England—to study the function of breast cancer susceptibility genes;

- AstraZeneca Pharmaceuticals, Alderley Park, England—to work, under a Cooperative Research and Development Agreement, on potential therapeutic targets among the tandem group of zinc-finger class proteins, for the treatment of inflammatory diseases;

- Radcliffe Infirmary, Oxford, England—to investigate MARCKS and MLP genes in lissencephaly syndromes;

- Guy's Hospital, University College, London, England—to study expression of beta glucocorticoid receptors in patients with steroid-resistant asthma; and

- Oxford Glycosciences, Abingdon, England—to investigate proteomics approaches to protein glycation in diabetes, as products that can be used as markers of disease control and complications. (A Cooperative Research and Development Agreement is being negotiated.)

Researchers at NIEHS and the Novartis Institute for Medical Sciences, London, England, worked together to explore the role of the ShcC adaptor protein in regulation of receptor tyrosine kinase signaling in primary neuron cultures. Because of the restricted expression of ShcC in neurons, the researchers are testing whether these ShcC domains are able to inhibit RTKs present in neurons. The research group at the Novartis Institute for Medical Sciences has been microinjecting cells with expression constructs encoding the individual ShcC domains, to

assess their ability to inhibit particular RTKs in primary neuron cultures.

## Taiwan

Scientists at NIEHS and the National Cheng Kung University, Taichung and Tainan, collaborated on psychiatric and developmental follow-up of children who had transplacental exposure to PCBs. The scientists published a report on the effects of PCBs on reproductive health in humans, in the *International Journal of Epidemiology*.

## Multicountry Studies

The Chief, Toxicology Operations Branch, NIEHS, has been involved in discussions with the consortium of European Researchers, which is performing a series of cancer studies in rodents to examine the effects of radio frequencies used in cellular telephone transmissions. The consortium is planning the initial studies and is receiving funding from the European Union and manufacturers of cellular telephones, who have provided advice on study design and have explored options for recruiting study participants.

An NIEHS investigator participated in a collaborative project to compare PCB levels across studies of human neurodevelopment. This joint research involves investigators from the University of Quebec Central Hospital, Beauport; the University of Odense, Denmark; the University of Düsseldorf, Germany; and Erasmus University, Rotterdam, the Netherlands.

A researcher at NIEHS continued his ongoing joint work with researchers at Konstanz University, Germany, and the Hungarian Academy of Sciences, Budapest, on the application of mass spectrometry to biological problems, especially epitope mapping of antibodies by mass spectrometry.

Scientists at NIEHS, the Wuhan Public Health and Anti-Epidemic Station, China, and the National Institute of Public Health and Hospital Infantil Fredrico Gomez, Mexico City, Mexico, are collaborating to study genetic and environmental factors in childhood respiratory disease.

## Grant Review

A staff member from the Laboratory of Molecular Carcinogenesis, NIEHS, was a reviewer of grants for the British Columbia Health Research Foundation, Burnaby; the Well-

come Trust, London, England; the Human Frontiers in Science Program, Strasbourg, France; and the Italian Ministry for Universities and Research, Rome, Italy.

A scientist in the Laboratory of Reproductive and Developmental Toxicology, NIEHS, chairs a grant applications review panel for the National Cancer Institute of Canada. FY 00 was the 2nd year of a 3-year commitment.

A researcher in the Epidemiology Branch, NIEHS, reviewed applications for establishment of research units for the Medical Research Council of South Africa, Cape Town, and reviewed grant proposals for the Northern Contaminants Program Secretariat, Department of Indian Affairs and Northern Development, Hull, Quebec.

### Activities With International and Multinational Organizations

A scientist in the Toxicology Operations Branch, NIEHS, was invited by the World Health Organization (WHO) to serve as a member of the 7<sup>th</sup> Review Board on Concise International Chemical Assessment Documents, which met in Helsinki, Finland, in June, 2000.

An investigator in the Laboratory of Toxicology serves as a member of the WHO task force established to facilitate the collaborations in, and to seek funding for, research in Occupational and Environmental Factors Associated with Autoimmunity.

The Chief, Laboratory of Molecular Genetics, served on the executive board of the International Genetics Federation. The federation mainly chooses the location of and exercises oversight over the International Congresses of Genetics.

A researcher in the Laboratory of Reproductive and Developmental Toxicology serves as a member of the Advisory Committee, Japanese Testis Workshop, and as an ad hoc reviewer of research grants for funding agencies in Australia, Canada, and Italy.

The Chief, Laboratory of Environmental Pathology, participated in the Safety Working Group of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products, at the invitation of the U.S. Food and Drug Administration. The charge of the group is to develop international guidelines for safety testing for residues of veterinary drugs in human food. Separate

guidelines are being developed for toxicity to genetic elements and to the reproductive system, subacute and chronic toxicity, and carcinogenicity.

The Chief, Laboratory of Environmental Pathology, also participated as a member of International Cooperation on Harmonization of Technical Requirements of Veterinary Products, with observers from governmental agencies in Australia and New Zealand. The two VICH meetings he attended were in Brussels, Belgium, in October 1999, and in Tokyo, Japan, in April 2000.

### Extramural Programs

A large portion of NIEHS financial resources is used for extramural programs including grants, cooperative agreements, and contracts that are awarded competitively to academic and research institutions. The Division of Extramural Research offers a broad range of research opportunities for collaborations with foreign scientists. In FY 00, research collaboration took place between U.S. and foreign scientists in Argentina, Australia, Azerbaijan, Bangladesh, Canada, Chile, China, Denmark, Faroe Islands, France, the Gambia, India, Italy, Japan, Mexico, Norway, the Seychelles, Singapore, South Korea, Sweden, Switzerland, the United Kingdom, and Taiwan.

### Research Grants

Research support was provided for the following projects that include a foreign component:

- funding to the International Agency for Research on Cancer (IARC) for travel and subsistence of non-U.S. Government participants in international conferences and for preparation, printing, and distribution of IARC publications;

- support of WHO's International Program on Chemical Safety;

- development of methylation-specific methods for polymerase chain reaction that allow examination of methylation status of various cancer-related genes, for detection of chemical-specific methylation patterns in genes of lung and bladder tumors from patients in areas where arsenic is endemic (e.g., Argentina, Chile, and India);

- investigation of the effects of arsenic ingestion on risk for lung cancer and non-malignant chronic respiratory disease in populations in Argentina, Chile, and India;

- Australian study of the hypothesis that mitochondrial DNA in human spermatozoa is more susceptible to oxidative damage than nuclear DNA and therefore may serve as a sensitive biological marker (biomarker) for genomic damage in spermatozoa, with the goal of establishing a reliable sperm-based method for assessment of environmental risk, for use in clinical and epidemiologic studies;

- a project in Azerbaijan (a) to establish the relationship between among release of chemicals into the environment, exposure of a population, and the probability of an adverse health outcome and (b) to improve methods for assessment of risk from exposure to complex mixtures and for remediation;

- study of a cohort of 10,000 adults from Sonargaon, Bangladesh, who have been exposed to a wide range (from <10 to >1,000 mg/L) of inorganic arsenic in drinking water, to prospectively examine the short-term and intermediate-term health effects of such exposures;

- exploration of the effects of exposure to inorganic arsenic from drinking water in pregnant women and children living in Bangladesh;

- analyses to measure inorganic arsenic in samples of water, soil, and sediment, and in blood from residents of two subprojects in Bangladesh;

- study of biomarkers of exposure to arsenic, skin lesions, skin and bladder cancer, and heritable susceptibility to this metal in two populations: in an area of Bangladesh recently described as having extremely high exposures from contamination of drinking water and in Taiwan, where remediation efforts have resulted in reduction in arsenic exposure to ranges of one to three times that in most U.S. communities;

- collaboration with a researcher from Canada, to identify biomarkers of exposure and susceptibility to and toxicity from halogenated PCBs in a highly exposed North American Inuit population;

- work with a Canadian researcher showing that the *Schizosaccharomyces pombe* rad12<sup>+</sup> gene is a structural orthologue of the human BLM gene, with mutations leading to Bloom syndrome, and study of the mechanism of function of these genes, based on the hypothesis that the rad12<sup>+</sup> and BLM

gene products negatively regulate the DNA replication checkpoint control pathway;

- study that includes a Canadian researcher, to investigate lung disease in children in rural areas, many of whom are exposed to endotoxin and grain dust;

- collaboration with a Canadian researcher to investigate (a) the mechanism by which scatter factor protects epithelial and carcinoma cells against apoptosis at the levels of signal transduction from the c-Met receptor and (b) modulation pathways involved in apoptosis, cell-cycle progression, and DNA repair;

- study of the relationship of exposure to PCBs and thyroid function and development of the central nervous system in infants of the native Inuit population in Canada and extension of this study to a cohort of Greenland Inuit, by Danish investigators;

- examination of the relationship between airborne acidic air pollutants and the respiratory health of approximately 3,300 older adolescents living in 15 communities in the United States and Canada;

- study in China to determine whether biomarkers of aflatoxicosis caused by consumption of aflatoxin-contaminated foods can be modulated by ingestion of oltipraz or chlorophyllin;

- comparison of reproductive function in two populations in China—one in a highly industrial area with multiple sources of exposure to lead and one in a rural area with few opportunities for exposure to lead;

- study that is part of a larger study by the National Cancer Institute, NIH, to investigate the effects of moderate-to-high occupational exposure to benzene on chromosomal defects in sperm and semen quality in a cohort of approximately 50 Chinese men who were exposed to benzene and 40 who were not exposed;

- molecular biology and epidemiologic study to identify specific chromosome alterations in Chinese workers exposed to benzene;

- epidemiologic study of individuals in China who have been exposed to dithiocarbamates, known neurotoxicants, to delineate potential interactions of dithiocarbamates and their decomposition products within biological systems and to determine both the relevance of these interactions as

mechanisms of toxicity and their usefulness as biomarkers of exposure;

- studies (a) to develop and validate molecular biomarkers of aflatoxin exposure in carriers and noncarriers of hepatitis B virus in Qidong Province, China, and the Gambia; (b) for follow-up of a prospective cohort in rural China, to examine the relationships and interactions among levels of aflatoxin biomarkers, intrinsic risk factors, and disease outcome; and (c) to determine the impact of primary prevention strategies in Guinea, by using a targeted strategy to reduce contamination in community settings, as evidenced by reduction of aflatoxin biomarker levels;

- study to refine and validate molecular biomarkers of human exposures to aromatic and heterocyclic amines and to use the markers to determine the influence of heterocyclic amines on the risk of colon cancer and of aromatic amines on the risk of bladder cancer in smokers and nonsmokers in defined cohorts in China, Japan, and Singapore;

- follow-up studies to assess the neurobehavioral effects of prenatal exposure to methylmercury and PCBs on the developmental outcomes for the offspring on the Faroe Islands;

- collaboration with a French researcher to investigate the role of dietary carcinogens in colon carcinogenesis;

- an epidemiologic study to assess the risk of endometriosis in women exposed to high levels of dioxins after an explosion at a chemical company in Seveso, Italy, in 1976;

- a prospective study of (a) the composite roles of lead levels in bone and DMSA-chelatable lead and (b) the effect of modification by the aminolevulinic dehydrase genotype, in the prediction of important health outcomes in a population of battery makers exposed to lead, in South Korea;

- study in Mexico City, Mexico, to examine the effect that maternal bone stores of lead accumulated from environmental exposures have on fetuses during pregnancy and infants during lactation;

- investigation of biosurfactants as a means to enhance removal of heavy metals from contaminated soil in Mexico;

- longitudinal study of lead exposure and reproduction in married men and women in

Mexico, with use of K-x-ray fluorescence to measure lead levels in bone;

- a population-based, case-control study on the role of heredity and environment in the occurrence of cleft lip and palate in Norway;

- studies in the Seychelles to examine the neurodevelopmental effects of chronic, low-level methylmercury in cohorts of children exposed to the compound by eating fish;

- research project in the United Kingdom, to evaluate accumulation of both organic and inorganic contaminants in the biota of New Bedford Harbor, Massachusetts, a Superfund site;

- collaborative work to quantify exposure-dose relationships of three types of biomarkers that show promise for estimating the internal dose of metabolic products after exposure to the human carcinogen 1,3-butadiene, in a population of petrochemical workers in Taiwan, with some of the bioassay work performed in Sweden; and

- molecular biology and epidemiologic study in Taiwan, to assess the relationship between aflatoxin exposure, as quantified by aflatoxin B1-DNA adducts, hepatitis B status, and liver cancer.

### **International Meetings**

During FY 00, NIEHS scientists were involved in various capacities in international meetings as follows:

- invited speaker on breast cancer risks from environmental chemicals, at the Collegium Ramazzini, in Capri, Italy, in October 1999;

- plenary lecturer at the Annual Conference on Opioid Mimetic Analgesics, at Kobe Gakuin University, Japan, and at the 120<sup>th</sup> Annual Meeting of the Pharmaceutical Society of Japan, in Gifu, in March 2000;

- invited speaker at a symposium on genetic susceptibility at the meeting of the European Society of Toxicology and the meeting of the British Association of Cancer Research, in London, England, in September 2000;

- co-organizer and cochair of a session on the role of cytokines in lung fibrosis, at the International Colloquium on Pulmonary Fibrosis, in Stockholm, Sweden, in September, 2000; and

- co-organizer of the Timofeeff-Ressovsky Centennial Conference, held in Dubna, Russia, in September 2000. (Nicolai Timofeeff-

Ressovsky was a founder of molecular biology, a leading geneticist, and the founder of radiation ecology in the former Union of Soviet Socialist Republics.)

In addition, NIEHS scientists participated in various capacities in planning future meetings as follows:

- served on the organizing committee of the 5<sup>th</sup> International Conference on Lactoferrin, to be held in Alberta, in May 2001;

- co-organizer of the meeting on the Epidemiology of Occupational and Environmental Factors Associated With Autoimmunity, sponsored by WHO's International Program on Chemical Safety, to be held in Bilthoven, the Netherlands, in May, 2001; and

- involved in planning the U.S.-European Workshop on Gene-Environment Interaction: Research at the Interface of Toxicology and Epidemiology, to be held in Munich, Germany, in September 2001.

### **Intramural Programs and Activities**

The NIEHS Division of Intramural Research conducts basic and applied research into the effects of environmental exposures on biological systems and human health, on the identification of susceptible human subpopulations, and on the interaction among the environment, genetics, and age. This research is often long term, high risk, and collaborative in nature, and it involves unique components, such as the NIEHS contribution to the National Toxicology Program, epidemiologic studies of environmentally associated diseases, and intervention and prevention studies to reduce the effects of exposures to hazardous environments. The Division of Intramural Research addresses the environmental component of many diseases. Specific environmental agents often play a role in multiple diseases and do not stop at national boundaries. The scientific disciplines represented within the Institute

include basic biological research at the cellular and molecular levels, classic toxicology, environmental epidemiology, clinical studies, and qualitative and quantitative risk assessment. This research is carried out in 17 Laboratories and Branches.

In FY 00, the Division offered a broad range of research opportunities for foreign scientists and hosted more than 80 Visiting Fellows, Visiting Associates, Visiting Scientists, and Guest Workers from 18 countries and Taiwan. These scientists came from the following countries: Argentina, Australia, Belarus, Brazil, Canada, France, Germany, India, Ireland, Italy, Japan, Korea, the Netherlands, Poland, Russia, Slovakia, the United Kingdom, and Venezuela.